Appendix A
Additional Publications

Code of Federal Regulations, 21, Parts 800 to 1299. Published yearly.

Premarket Approval (PMA) Manual, FDA 87-4214.

Premarket Approval (PMA) Manual Supplement, FDA 91-4245.
Medical Device GMP Guidance for FDA Investigators, FDA 84-4191.

Device Good Manufacturing Practices Manual, FDA 87-4179.

Investigational Device Exemptions - Regulatory Requirements for Medical Devices, FDA 90-4159.

Labeling - Regulatory Requirements for Medical Devices, FDA 90-4203.

Standards

ISO 11134: Sterilization of health care products - Requirements for validation and routine control - Industrial moist heat sterilization.

ISO 11135: Medical devices - Validation and routine control of ethylene oxide.

ISO 11137: Sterilization of health care products - Requirements for validation and routine control - Radiation sterilization

ISO 5840: 1989, Cardiovascular implants - Cardiac valve prosthesis.

ISO 10993-1: 1992, Biological evaluation of medical devices - Part 1: Guidance on selection of tests.

ISO 10993-2: 1992, Biological evaluation of medical devices - Part 2: Animal welfare requirements.

FDA Guidance Documents

Guideline for the Monitoring of Clinical Investigations.

Guideline on Validation of the Limulus Amebocyte Lysate Test as an End-Product Endotoxin Test for Human and Animal Parenteral Drugs, Biological Product, and Medical Devices, (December, 1987).

Statistical Aspects of Submission to FDA: A Medical Device Perspective, (1982).

Guidelines on General Principles of Process Validation, (May, 1987)

Guidance for Preparation of PMA Manufacturing Information, (1992).

Guidance Document for the Evaluation of Pyrolytic Carbon, (1990).

Mechanical Valve Impact Factor - Rough Draft Protocol.

Guidance for the Preparation of the Annual Report to the PMA Approved Heart Valve Prosthesis, (September 1990).

Blue Book Memorandum

Device Labeling Guidance, General Program Memorandum #G-91-1, (March 8, 1991).

PMA Compliance Memorandum, PMA Memorandum #P91-3, (May 3, 1991).

Other

Conditions of Approval, (November 5, 1993). As established by the ODE Premarket Approval Staff.

Appendix B
Pyrolytic Carbon:
Additional Information

Materials Characterization

Property values and/or specification limits (where applicable):

Substrate density
Substrate composition
Substrate microstructure
Substrate coefficient of thermal expansion
Substrate Young's modulus
Substrate flexural strength
Substrate Poisson's ratio

Coating density
Coating composition
- alloy content
- alloy distribution

Coating microstructure
Coating crystal structure
- carbon crystallite size
- carbon lattice spacing
- alloy (e.g. silicon carbide) crystallite size

Coating thickness
Coating coefficient of thermal expansion
Coating Young's Modulus
Coating flexural strength
Coating Poisson's ratio

Microhardness
Anisotropy factor
Critical surface tension
Surface finish
Tensile strain to failure
Fracture toughness

Also, for each of the parameters, indicate which parameters are routinely measured as part of the manufacturing quality assurance program. It is left to the manufacturer to determine the most suitable test methods for obtaining this information, and to demonstrate that the particular test method chosen will measure the desired property with sufficient sensitivity to identify variations in the manufacturing process which may effect valve performance. To ensure that the reported properties are truly representative of the current manufacturing process, the values reported must be measured directly on parts manufactured by the sponsor and not cited from the literature.

For additional information, see the "Guidance Document for the Evaluation of Pyrolytic Carbon", (1990).

Manufacturing/Quality Assurance Issues

Small changes in process control parameters affect the resulting physical and chemical characteristics of the pyrolytic carbon coating. Therefore, it is necessary to establish that the process is sufficiently controlled to produce consistent product.

Heterogeneous regions (e.g. soot pockets, porosity, etc.) in the coating can effect the physical properties of the entire component. Therefore, it is necessary to describe the accept/rejection criteria for these parameters, as well as establish that coating process control and quality assurance methods are sufficiently sensitive to avoid or identify any defects.

Process Validation

It is necessary to validate the coating process in which pyrolytic carbon is deposited on graphite substrates in a fluidized bed reactor. The purpose of this study is not to determine if the manufacturer has optimized their process, but rather to establish that the process is well controlled, well characterized, and that there is an understanding of what will happen to the critical material properties (as listed below) as in-tolerance and out-of-tolerance variations in process parameters occur.

The following independent (input) variables must be investigated, or a justification for not investigating them must be provided:

- Bed temperature;
- Gas flow;
- Composition and flow of feed gases;
- Bed size, weight, or surface area;
- Part geometry or mass.

The following dependent (output) variables must be investigated, or a justification for not exploring these parameters must be provided:

- Coating density;
- Microhardness;
- Alloy content;
- Flexural strength;
- Strain to failure;
- Young's modulus;
- Fracture toughness.

The appropriate use of response surface methods and/or multivariate quality control must be utilized in order to couple the list of input parameters with the output parameters and

properties. The proper model must include at least linear, quadratic, and linear cross product terms.

Fatigue Testing

In accordance with the policy established by ODE senior staff on August 7, 1990, all pyrolytic carbon heart valves must be tested to establish that fatigue failures will not occur under *in vivo* loading conditions. This requirement is based on observations which indicate that ceramics in general, and specifically pyrolytic carbon, do fatigue[13]. Therefore, each manufacturer must complete a complete fatigue analysis on the pyrolytic carbon components of the device.

Appendix C
Sizing Stentless Heart Valves

The size of the stentless aortic valve is determined by placing the assembled valve into the appropriate orifice of a sizing gage, an example of which can be found in the attached figure. At the present time, sizing gages may not be available in all the tissue annulus diameters which will be marketed. All manufacturers must use appropriate sizing gages for the valve tissue annulus diameters they intend to market, even if this entails developing gages in tissue annulus diameters not currently available. The following criteria will assure uniform sizing of stentless aortic valves within the heart valve industry.

The valve annulus is aligned with the inner diameter of the gage orifice. The following criteria must be met: (i) there are no gaps greater than 0.5 mm between the valve annulus and the inner diameter of the gage orifice; (ii) the valve annulus is not constricted (e.g., crimped or crowded) by the gage orifice; and (iii) if the valve annulus is not circular, the valve must be internally pressurized with a pressure of about 10 to 20 mmHg until a circular annulus is achieved. Sizing must be conducted on a circular annulus only.

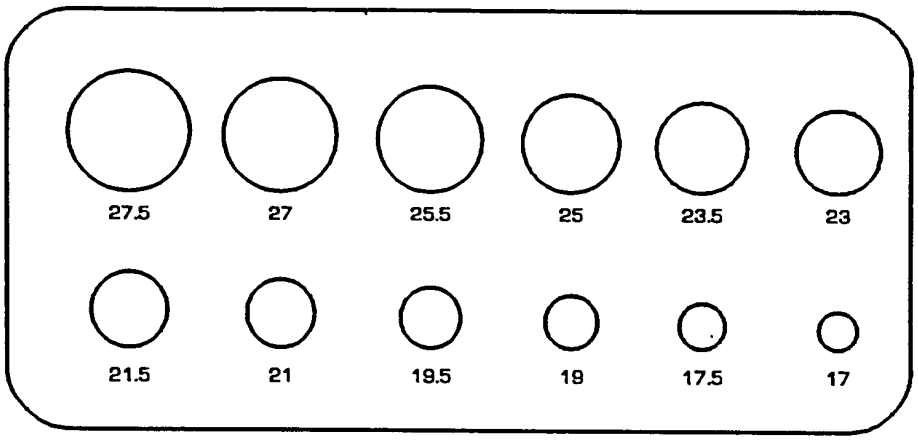

Figure 1 Sizing Gage for Stentless Heart Valves

Appendix D
Standardized Test Methods

Specifications for material for metal surgical implants. (Covers stainless steel, cobalt chrome alloys, and titanium alloys)	ISO 5832:Parts 1 - 8
Specification of surgical implants made from high density silicone elastomer	BS 3531: Part 16: 1985
Specifications for high-molecular mass polyethylene	ISO 3834
Density	ASTM D792
Physical and chemical properties	ISO 6474
Microstructure	ASTM E3, E112
Thermal expansion	ASTM E228
Tensile properties	ASTM D638, E8, E111, ISO R527
Breaking strength	ISO 5081
Tear out resistance	DIN 53 859 Teil 2
Flexural properties	ISO 178: ISO DP 178
Compressive properties	ISO CD 604
Dynamic mechanical properties	ISO DIS 6721-1 and -2
Stress Relaxation	ASTM D2991
Creep	ASTM D2990
Poisson's Ratio	ASTM E132
Hardness	ASTM E18, E92, D785
Wear	ISO 4586/2, ASTM D1044, D4060
Liquid diffusivity	ASTM D570
Water adsorption	DIN 53 923
Fatigue crack initiation and endurance limit (S/N curves)	ASTM E466, E468, E469, E739

Fatigue crack growth rates	ASTM E647
Fracture toughness	ASTM E399, E813

Appendix E
Hydrodynamic Testing
Test Chamber Requirements

Steady flow test chamber:

The chamber should be well characterized using a standard sized nozzle. The nozzle for forward flow testing is shown in figure 1, and the nozzle for backflow leakage is shown is figure 2.

Rigid mount pulse duplicator:

For performance evaluations that require the use of a pulse duplicator, the flow characteristics of the test apparatus shall approximate, as closely as possible, those of physiological flow.

Test apparatus for all pulsatile measurements shall conform to the requirements of ISO 5840, Cardiovascular Implants- Cardiac Valve Prosthesis.

Compliant aortic chamber:

For stentless porcine valves, the test chamber used for hydrodynamic and wear performance assessments must be constructed from compliant material and emulate an aortic root geometry, as shown in figure 3 below. A circular geometry is assumed for the supra aortic ridge. Except as excluded for a intact root prosthesis, two values of test chamber compliance must be used for both hydrodynamic and wear testing. These compliances must be 4% $\pm$ 1% and 16% $\pm$ 4%, as measured at a transmural dP/dt of +400 $\pm$ 100 mmHg/s and remain within these limits over the pressure range from 40-160 mmHg. These compliances must be established without a prosthesis mounted. Testing over the pressure range from 40-160 mmHg may require two or more test chambers for different pressure regions.

In the compliant-chamber duplicator, the pressure measurements must be made at or within 5 mm downstream of the supra-aortic ridge, and compliance must be determined at the same location. The cross sectional areas of the test section at the downstream and upstream pressure measurement sites must be the same at 100 mmHg. Intact root type prosthesis would be considered an exception to the test condition of equal area upstream and downstream.

Chamber compliance, (C), is defined as the change in external diameter at the supra-aortic ridge over a 40 mmHg pressure increase, divided by the diameter at the supra-aortic ridge at 40 mmHg gage pressure.

$$C = \frac{D_2 - D_1}{D_0}$$

where D_0 is the external diameter at 40 mmHg;
D_1 is the external diameter at some higher pressure, P_1; and
D_2 is the external diameter at pressure P_2, 40 mmHg higher than P_1.
The units of compliance are stated as percent, but percent per 40 mmHg pressure difference is implied.

Exclusion for intact root

For intact root prosthesis, it is possible that the non-compliant nature of the root may be the dominant compliance in the implant/chamber system. Under these circumstances, it may not be necessary to consider chamber compliance in the in vitro testing. If chamber compliance measurements, with and without the prosthesis attached, as described in Appendix F, indicate that the compliance with the prosthesis attached is significantly less than without the prosthesis attached, it can be assumed that the prosthesis compliance is dominant, and testing in compliant aortic chambers is not required. In this case, a configuration involving two sets of tubular segments, whose compliances are 4% and 16%, and which are attached at the inflow and outflow edges of the root may be used for the in vitro testing. It must be shown that the length of these segments is sufficient to eliminate the possibility of artifactually constraining the supra-aortic ridge. Furthermore, if it can be experimentally demonstrated that the compliance of the segments does not affect hydrodynamic performance of the valve, then testing with segments of a single compliance is allowed.

Compliance Effect Validation

Complete testing of stentless valves in 16% chambers is not required if data can be provided that shows that valve performance is not a function of chamber compliance. This can be shown by providing the following data for both chambers: pulsatile flow regurgitation measurements, as described in **section VI.A.2.a.(4)** at a cardiac output of 5 l/min, at three beat rates in the range between 45 and 120 beats/min. The largest tissue annulus diameter valve must be used in the testing, and the valve must be sized at 100 mmHg.

Open atrial chamber (cavitation):

The open atrial chamber shall be open, rigid, of circular or square cross section, and have a cross sectional area of at least 75 cm^2. When the chamber is filled, it must have a mean pressure at the valve of 7 mmHg. The pressure sensor shall be mounted in the ventricular chamber 3.5-5.0 cm from the valve and centered with respect to the valve.

Table 1
Test Chambers

Type of Test	Mechanical	Stented Tissue	Stentless Tissue
Steady Forward Flow	1	1	3
Steady Backflow Leakage	1	1	3,4
Pulsatile Flow Pressure Drop	2	2	3
Pulsatile Regurgitation	2	2	3,4
Flow Visualization	2	2	3,4
Cavitation Potential	5	6	6
Bernoulli Verification	2	2	3

1. steady flow chamber
2. rigid mount pulse duplicator
3. 4% compliant aortic chamber
4. 16% compliant aortic chamber
5. atrial chamber/or other appropriate chamber
6. not required

Note: See above for exclusion for intact aortic root prosthesis and when complete testing is not required in the 16% compliant chamber.

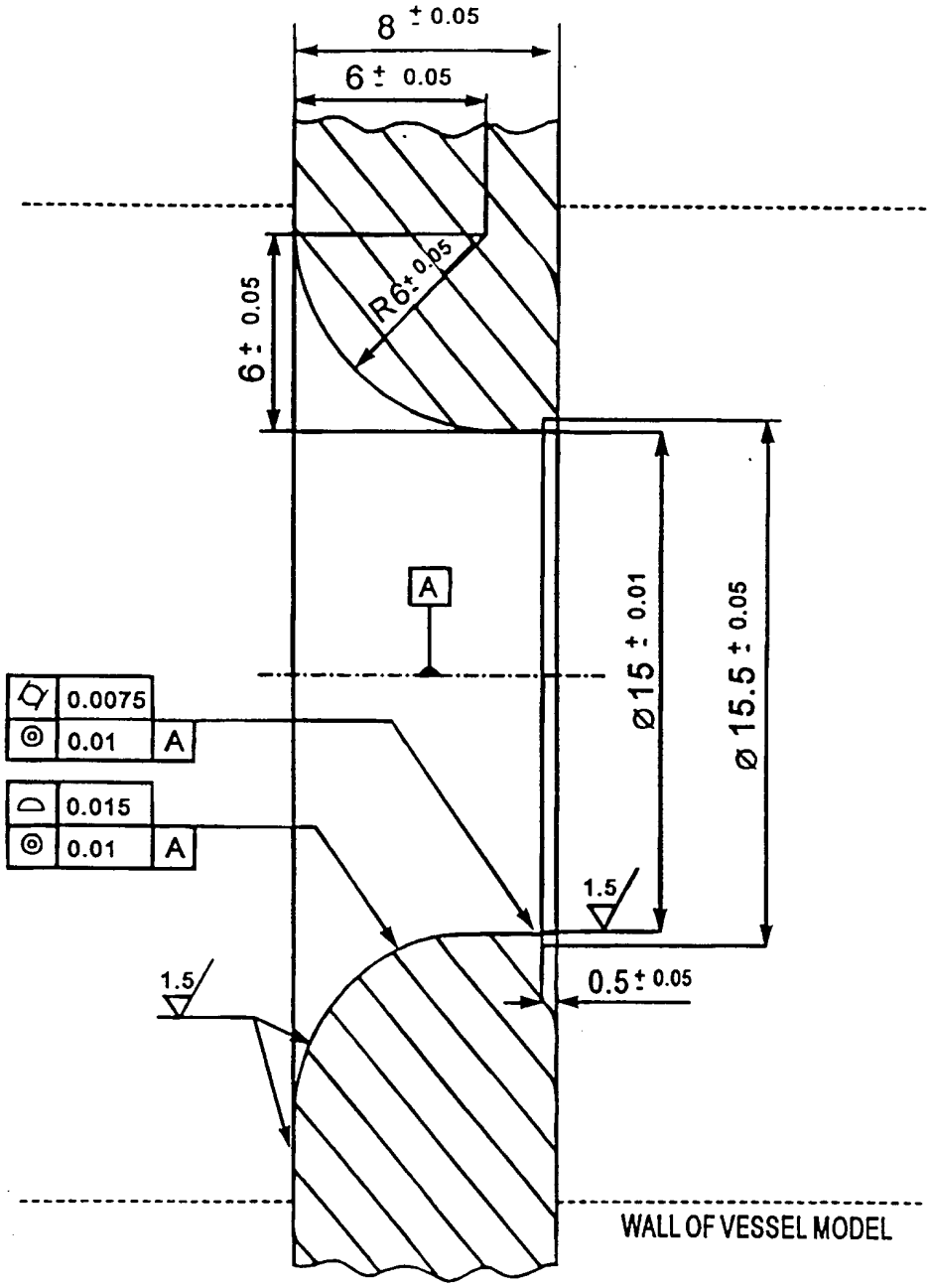

Figure 1. Standard nozzle, forward flow

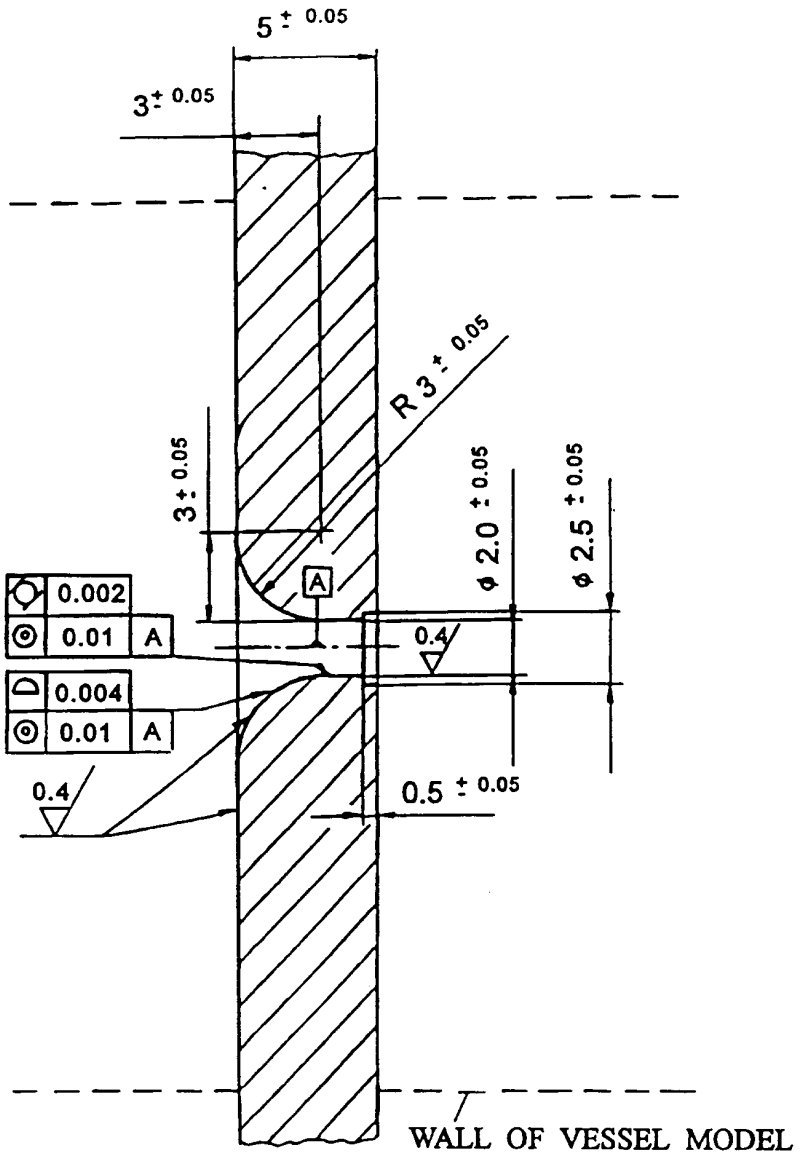

Figure 2. Standard nozzle, back flow

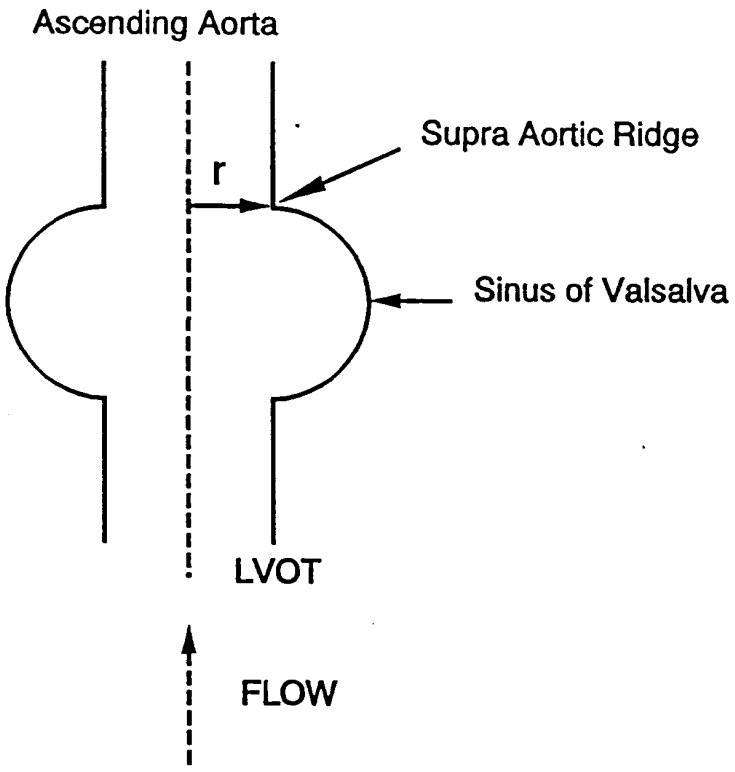

Figure 3. Compliant Chamber Configuration

Appendix F
Hydrodynamic Testing
Test Chamber Verification
Report Requirements

Steady flow test chamber:

The test report shall include a description of the test apparatus, including its conformance with the recommendations provided in appendix E.

Rigid mount pulse duplicator:

The test report shall include a discussion of how the flow characteristics of the test apparatus approximate physiological flow, and/or an indication that the pulse duplicator conforms with the requirements of ISO 5840.

Compliant aortic chamber:

The test report shall included a description of the chamber, and the compliant-chamber characterization data, as described below.

Data characterizing the chamber must be collected without the prosthesis mounted, and for both the 4% and 16% compliant aortic chambers, and under the following conditions:
(i) diameter versus pressure curves taken at transmural pressures ranging from 40 - 160 mmHg, at two transmural (dP/dt)s: (1) +400 $\pm$ 100 mmHg/s; (2) and a value representative of the maximum (dP/dt) expected during wear testing;
(ii) for both the 4% and 16% compliant aortic chambers, calculated values of compliance at p_2 = 80, 120, and 160, mmHg, at both (dP/dt)s defined above;
With the prosthesis mounted, and for both the 4% and 16% compliant aortic chambers:
(i) diameter versus pressure curves taken at transmural pressures ranging from 40 - 160 mmHg, at two transmural (dP/dt)s: +400 $\pm$ 100 mmHg/s; and a value representative of the maximum (dP/dt) expected during wear testing;
(ii) for both the 4% and 16% compliant aortic chambers, calculated values of compliance at p_2 = 80, 120, 160, and 200 mmHg, at both (dP/dt)s defined above.

Open atrial chamber (cavitation):

The test report shall included a description of the chamber, and the test protocol which includes the frequency response of the pressure sensor used. If conditions other than those recommended are deemed more appropriate for the study valve, provide evidence for this and fully describe the test conditions and the rationale for the procedures chosen. Examples of other conditions would include the use of compliant valve mounts or testing valve other than the largest tissue annulus diameter.

Appendix G
Hydrodynamic Testing
Test Fluids

Test fluids used in hydrodynamic testing shall be blood-analogs with controlled density and viscosity. For example, a water-glycerol mixture whose nominal density is 1.10 g/ml at room temperature with a viscosity of 3.0 to 3.5 cP is an acceptable blood analogue. Small amounts of fungicide, algicide, or other antibacterial agents may be added, as long as the fluid has the appropriate physical properties, and the additives do not adversely affect the properties of the tissue in the prostheses. A physiological saline mixture whose nominal density is 1.005 g/ml with a viscosity of about 1.0 cP at room temperature may be substituted for the blood analogue in the hydrodynamic studies under one of the following conditions: (i) steady flow pressure drop, steady flow backflow leakage, pulsatile flow pressure drop, and pulsatile flow regurgitation testing on mechanical and stented bioprosthetic valves; (ii) steady flow pressure drop, steady flow backflow leakage, pulsatile flow pressure drop, and pulsatile flow regurgitation testing on stentless valves if the detrimental effects of glycerin upon anti-mineralization treatments has been demonstrated; (iii) steady flow pressure drop, steady flow backflow leakage, pulsatile flow pressure drop, and pulsatile flow regurgitation on stentless valves if the detrimental effects associated with bacterial contamination has been either referenced or validated with experimental data. If the use of saline is to be justified for the testing of stentless valves, experimental data over the full pressure range and at each specified beat rate for one of the largest and one of the smallest valves for each model, studied in saline and in glycerine must demonstrate reasonable performance comparability. In all cases (tissue and mechanical), wear testing, cyclic failure, and flow visualization may be conducted in buffered saline with a nominal density of 1.005 g/ml at room temperature, and a viscosity of about 1.0 cP at room temperature.

Table 1
Test Fluids

Type of Test	Mechanical	Stented Tissue	Stentless Tissue
Steady Forward Flow	2	2	1
Steady Backflow Leakage	2	2	1
Pulsatile Flow Pressure Drop	2	2	1
Pulsatile Flow Regurgitation	2	2	1
Flow Visualization	2	2	2
Cavitation Potential	1	3	3
Bernoulli Verification	1	1	1
Wear	2	2	2

1. Blood analog
2. Physiological saline
3. Not required

Note: See above for conditions under which physiological saline may be substituted for blood analog.

Appendix H
In Vitro Cavitation Analysis of Mechanical Prosthetic Heart Valves

Determine the minimum dP/dt that causes bubble formation. Three of the largest valves, and one each of two reference valves of different manufacture or style, shall be tested. Ideal parameters for the chamber geometry, the valve mounting, and other test conditions have not been established, however a recommended chamber geometry is provided in appendix F.

dP/dt must be averaged over the last 20 msec before mitral valve closure. Time of closure has been defined to be coincident with the principle pressure spike associated with leaflet impact. For bileaflet valves, the closing of the second leaflet should be considered. Visual images must be collected at the threshold dP/dt. The test should be conducted up to a maximum of 1200 mmHg/sec, with a resolution of 100 mmHg/sec. If neither the test not reference valve shows bubble formation within this range, the maximum value should be increased to 1000 mmHg/sec. The system must be capable of visualizing 0.5 mm diameter bubbles, existing for 0.02 msec, over the entire atrial surface of the valve.

Valves shall be rigidly mounted in the mitral position of a left heart simulator or other test system which is capable of simulating mitral flow under conditions at valve closure. The test fluid must be a blood analogue. All tests must be run at a nominal pulse rate (70 beats/min) with systole occupying 35% $\pm$ 2% of the cycle time, and a mean ventricular pressure during aortic forward flow of 100 mmHg. The fluid should be held at 37C.

Changes in dP/dt can be accomplished by changing ventricular chamber compliance or stroke volume. For a particular test system, if it is necessary to let the mean ventricular pressure rise above 100 mmHg, or if it is necessary to have systole occupy less than 35% $\pm$ 2% of the cycle time in order to achieve the necessary dP/dt, then this must be noted.

Any characterization of the test fluid, as to its content of nucleation sites for cavitation or any treatment of the test fluid to control the number of such sites should be described.

Data must be presented as follows: (i) the minimum value of dP/dt (the "threshold value", for each valve tested, at which bubbles were identified, (ii) a clear hard copy of the visual image of the bubble field as well as a pressure profile for an entire beat and an expanded profile encompassing the valve closing pressure spike $\pm$ 50 msec, associated with the threshold dP/dt.

Interpretation

It is understood that a valve can produce cavitation bubbles in area where pyrolytic carbon erosion does not occur. It is necessary to consider the results of the cavitation threshold testing in conjunction with a knowledge of areas where erosion does occur. This information must be obtained from wear testing and cyclic failure mode testing. Information from explants (which have been implanted over long periods of time) may also provide useful information. Therefore, cavitation erosion that occurs on the pyrolytic carbon must not be at the same place as the failure mode initiation point, or the long term durability of the valve is questionable.

Appendix I
Impact factor determination

Bench tests conducted at CDRH's Office of Science and Technology laboratory indicate that in a pulse duplicator, the value of the stress present at the time an occluder impacts an orifice in a mechanical valve can be as high as seven times the static applied (peak systolic) pressure (depending on the pulse duplicator). These experiments also showed that this "impact factor" is a function of specific valve design. Therefore, for each valve, it is necessary to determine the magnitude of this transient load, as well as the time it occurs (in relation to peak systolic pressure) for inclusion in the stress analysis. For a mitral valve, a conservative peak systolic pressure and mean aortic pressure must be utilized in this analysis.

It is theoretically possible that this value could be calculated using standard hydrodynamic theories, such as a water hammer analysis. However, manufacturers must be cautioned that it will be necessary for the analysis to be conservative, and that all assumptions made during the analysis must be adequately justified. Furthermore, it will be necessary to validate the model with in vitro or in vivo data to show that the model will predict observed behaviors.

It is also possible to measure the magnitude of this impact factor in a pulse duplicator. The rigid mounting system in the pulse duplicator will serve to ensure that the measured stresses/strains or pressure spikes are higher than those experienced in vivo. If the value of the "impact factor" measured in a pulse duplicator can be incorporated into the lifetime calculations, and the minimum assured lifetime is sufficiently long, this type of analysis is acceptable. However, it is necessary that the experimental equipment be sufficiently sensitive to detect these highly transient effects.

If the impact factor measured in the pulse duplicator, which can be assumed to be higher than that which will be present in vivo, is sufficiently high to lower the calculated lifetime of the valve to unacceptably low levels, it will be necessary to determine the value of the "impact factor" in a compliant mount pulse duplicator or in vivo.

While it may not be possible to measure dynamic stress directly, it is possible to measure other parameters (e.g. dynamic pressure or strain) which can be calibrated to stress. For example, it is possible to calibrate pressure to stress under static conditions in a pulse duplicator data. Pressure measurements of the transient stress must be taken within several mm of the area of contact, and must be obtained with pressure transducers with an adequate frequency response.

If in vivo testing is chosen, an appropriate animal model must be chosen, and the choice must be justified. The study design must also consider which implant position (aortic or mitral) would represent worse case loading for the particular valve design under consideration. Pressure waveforms, strain, etc. must be measured in the left ventricle and atrium, or on the valve directly, using laboratory equipment and data acquisition techniques of sufficient sensitivity to detect the transient effect.

The analysis must include a detailed description of the apparatus used, including a discussion of the sensitivity and fidelity of both the equipment used to collect the data and the entire data acquisition package. Additional information can be found in the "Mechanical Valve Impact Factor - Rough Draft Protocol". This document provides specific information on the types of equipment as appropriate. However, manufacturers must consider the following: (i) the largest orifice diameter valve does not always experience the largest loads; (ii) the region of maximum static stress is not necessarily the region of maximum impact stress.

Appendix J
Explant Analysis

When the valve is explanted, the valve must be excised and the residual blood rinsed from the valve surfaces and sewing ring by gently agitating in sterile Ringer's lactate solution. If the prosthetic valve is obtained at necropsy, in situ photographs of both the inflow and outflow tracts must be taken before the valve is removed from the heart. Primary fixation is accomplished using 4% formaldehyde/ 1% glutaraldehyde in 0.1 M phosphate buffer (pH 7.4) for morphological studies or an intermediate level disinfectant solution consisting of 70% ethanol in 0.1 M phosphate buffer (pH 7.4) if in vitro performance testing is to be completed.

During the gross examination, the excised valve must be completely submerged in fixative. Observations (e.g., tissue overgrowth, fibrous sheath, thrombus, tissue abrasion, materials wear) must be completely documented with the aid of a dissecting microscope and photograph. Where appropriate, radiographic studies must be completed to identify wear (on mechanical valve) and calcification (of tissue valves).

The serial number must be provided for all valves. For mechanical valves (with the exception of valves with polymeric leaflets), the examination must encompass a determination of poppet/occluder excursion and seating, including any interferences (e.g., fibrous sheath, cloth wear, thrombi) that may compromise poppet/occluder motion. The dissecting microscope should be used to identify any defects, fractures, asymmetries, sites of wear, and poppet/occluder variance. An examination with a scanning electron microscope, or a profilometer, should be used to identify any surface topology aberrations. If asymmetries are identified, variance from manufacturing specifications must be determined using a profile projector.

For tissue valves, and valves with polymeric leaflets, in addition to the appropriate information listed above for the mechanical valve, the examination must include an assessment of cuspal excursion and the presence of leaflet fenestrations, tears, hematomas, and calcified nodules. In addition, one half of each leaflet must be used for the quantitative determination of inorganic calcium and phosphate. Histological evaluation must be completed on each leaflet (minimally, one specimen sampled from the mid-portion of the leaflet, free edge to base, flat embedded and studied in cross section). This histological examination must establish the morphology of the tissue/valve interface, as well as initially assess leaflet calcification and histopathology. The recommended minimal light microscope protocol must include glycol methacrylate sections stained with hematoxylin and eosin, von Kossa (calcium phosphate) and unstained slides retained for additional studies as indicated.

The unused portion of each prosthetic valve leaflet must be retained in fixative for additional histological studies, as deemed necessary.

Where possible, hydrodynamic studies should be conducted on explanted valves. Pulsatile flow pressure drop and regurgitation measurement should be obtained, and presented as mean systolic (diastolic) pressure versus the root mean square of the systolic (diastolic) flow rate. Systole must be defined by the flow, and will include some negative pressure drop. Regurgitation measurements should included closing volume and leakage volume. However, before conducting in vitro performance testing, the potential occupational risk to laboratory personnel must be weighed. This type of testing should not be conducted if appropriate cautionary measures are not available.

Appendix K
Objective Performance Criteria for Heart Valve Studies

	Mechanical[1]	Tissue[1]
Thromboembolism	3.0	2.5
Valve Thrombosis	0.8	0.2
All Hemmhorage	3.5	1.4
Major Hemmhorage	1.5	0.9
All Perivalvular Leak	1.2	1.2
Major Perivalvular Leak	0.6	0.6
Endocarditis	1.2	1.2

NOTES
1. Values in % per valve-year.

Appendix L
Definitions of Complications for Heart Valve Studies

Operative mortality	Death from any cause during or after implant, within 30 days if the patient is discharged or within any interval if the patient is not discharged.

Morbid Events

Angina	An attack of brief paroxysmal chest pain due to myocardial ischemia.
Anticoagulant related hemorrhage	Any episode of internal or external bleeding in patients receiving anticoagulants and/or antiplatelet drugs, including any episode of hemorrhagic tamponade. A prothrombin time at the time of the hemorrhage is required. These events must be reported as major or minor, as defined below.
Major:	An episode of internal or external bleeding which causes death, stroke, operation, or hospitalization, or requires transfusion. Examples are nosebleeds that require outpatient transfusion, cerebral bleeding which results in neurological damage and/or death, and gastrointestinal bleeding which requires hospitalization.
Minor:	All other episodes of internal or external loss of blood. Examples include nosebleeds that do not require transfusion, hematomas due to trauma or surgery which do not require transfusion, or minor ocular hemorrhage.
Arrhythmia	An alteration of the heart's rhythm from normal sinus rhythm which requires drug and/or pacemaker therapy.
Cardiac arrest	Permanent or temporary cessation of organized heart function, or precipitous drop in blood pressure sufficiently severe to require CPR or emergency defibrillation.
Endocarditis (prosthetic valve)	Any infection involving the replacement heart valve. The diagnosis of prosthetic valve endocarditis is based on customary clinical criteria including an appropriate combination of positive blood cultures, clinical signs (fever, new or altered cardiac murmurs, splenomegaly,

systemic emboli, or immunopathological lesion) and/or histologic confirmation of endocarditis at reoperation or autopsy. The organism involved should be identified. Secondary events related to endocarditis (hemolysis, perivalvular leak, thromboembolism, or thrombosis) should be recorded as such.

Heart failure — A new event in which the heart fails to meet the circulatory requirements of the body under differing physiological circumstances, and/or a state in which cardiac output is reduced relative to the metabolic demands of the body, assuming the evidence of adequate venous return. The event must be reported as valve related or non-valve related.

The most common causes of non-valve related heart failure are coronary artery disease, hypertension, valvular heart disease (due to a valve other than the study valve), cardiomyopathy, cor pulmonale, or congenital heart disease. Heart failure will be considered valve related if: the event is a new event which is not continued from a preoperative heart failure, and is caused by one of the following prosthesis valve-related events: anticoagulant related hemorrhage, endocarditis, hemolysis, nonstructural dysfunction, perivalvular leak, structural deterioration, thromboembolism, thrombosis, reoperation, or unknown causes.

Hemolysis — Anemia associated with laboratory evidence of red cell destruction. More specifically, the hemoglobin and hematocrit value fall below the lower limit of the cited normal range for those values. The haptoglobin value must be less than the lower limit of the cited normal range. The serum LDH value must be higher than the upper limit of the cited normal range. Elevated reticulocyte count may or may not be present. Events which are excluded are: those due to liver disease, myocardial infarction, or systemic infection. If the event is secondary to endocarditis, hemorrhage, perivalvular leak, thromboembolism, thrombosis, it should be reported as such. These events must be reported as clinically significant or not clinically significant, as defined below.

Not clinically significant: Does not require intervention

Clinically significant: Requires intervention

Myocardial infarction	An area of coagulation necrosis resulting from impaired oxygenation of the myocardium. Events that are excluded are: those in patients who possess normal coronary arteries or if the patient is less than 40 years of age (will be reported as thromboembolism events).
Nonstructural dysfunction	Any change in prosthesis function which results in stenosis or regurgitation at the prosthesis and which is not intrinsic to the prosthesis itself. Examples include: inappropriate sizing, and leaflet entrapment by suture and pannus. The diagnosis should be confirmed by examination of the explanted or damaged valve. Events which are excluded are: those associated with endocarditis, perivalvular leaks, and thrombosis.
Perivalvular leak	Any evidence of leakage of blood around the prosthesis (between the sewing ring and the native annulus). Diagnosis of perivalvular leak may be obtained from echocardiography, however definitive diagnosis is obtained at reoperation, explant, or autopsy. If the event is secondary due to endocarditis, it must be reported as such. Secondary events related to perivalvular leak (hemolysis, thromboembolism, or thrombosis) should be also be recorded as such. These events must be reported as major or minor, as defined below.
Minor:	Does not require surgical intervention.
Major:	Requires surgical intervention.
Structural deterioration	Any change in prosthesis function which results from an intrinsic abnormality that causes stenosis or regurgitation. The diagnosis should be based on an examination of the explanted or damaged valve. Examples include wear damage, stress fracture, leaflet escape, calcification, leaflet tear, and stent creep. Events which are excluded are: those associated with endocarditis, perivalvular leaks, and thrombosis.
Thrombo-embolism	Any thrombosis which migrates within the arterial circulation as evidenced by neurological or other deficit or loss of function, and any peripheral arterial emboli. The event will be described as permanent or transient and will be determined to be a central (cerebral) or a peripheral (other than cerebral) neurological deficit. Events which are included are: acute myocardial infarction that

occurs after operation if the patient possesses normal coronary arteries or if the patient is less than 40 years of age. Events which are excluded are: those which occur intraoperatively, or within 24 hours of surgery, due to myocardial infarction or stroke; any peripheral arterial emboli proven to have originated from another cause (e.g., atrial myxoma); failure to awaken from the surgical procedure; pulmonary emboli; or events due to proven ischemic disease of the extremities. If the event is secondary to hemorrhage, perivalvular leak, or endocarditis, it should be reported as such. Secondary events related to thromboembolism (hemolysis) should also be recorded as such.

Thrombosis (valvular) — Formation of a blood clot on any part of the prosthesis leaflets, orifice or sewing ring. The diagnosis should be based on an examination of the explanted valve, or during autopsy, although a diagnosis can be made by a clinical picture of the presence of thrombosis (lack of normal prosthetic valve sound; prolonged lowered blood pressure; loss of consciousness; cardiovascular shock) if the clinical diagnosis is accompanied by a confirming diagnostic test (echocardiography or angiography). If the event is secondary to hemorrhage, perivalvular leak, or endocarditis, it should be reported as such. Secondary events related to thromboembolism (hemolysis) should also be recorded as such.

Consequences of Morbid Events

Explant — Removal of the study valve for any reason.

Reoperation — Any operation to repair, alter, or replace the study valve. Included is reoperation for repair of perivalvular leak and explant. All reoperation is considered prosthesis-related.

Death — Permanent cessation of all vital bodily functions. Prosthesis-related death will include deaths caused by the following events: prosthesis thrombosis; thromboembolitic events; endocarditis; structural deterioration; nonstructural dysfunction; prosthesis-related heart failure; anticoagulant-related hemorrhage; death at reoperation; perivalvular leak; hemolysis; sudden unexplained death without autopsy which defines cause as other than prosthesis-related. Deaths

caused by heart failure in patients with advanced myocardial disease and satisfactorily functioning cardiac valves are excluded.

Additional Morbid Event for Required Postmarket Surveillance Studies

Unacceptable hemodynamics	An unacceptable movement of blood through the valve, as characterized by severe regurgitation or stenosis of the valve. The hemodynamic function of a valve becomes unacceptable when intervention to correct the problem is necessary.